Paper No. 23

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte OSCAR J. LLORIN, MATTHEW P. COLLIS, MICHAEL C. LITTLE, and JAMES M. HARRIS

Appeal No. 2002-0780
Application No. 09/128,340

ON BRIEF

Before, ADAMS, MILLS and GREEN, Administrative Patent Judges.

ADAMS, Administrative Patent Judge.

VACATUR and REMAND TO THE EXAMINER

On consideration of the record we find this case is not in condition for a decision on appeal. For the reasons that follow, we vacate[1] the pending rejection under 35 U.S.C. § 103 and remand the application to the examiner to consider the following issues and to take appropriate action.

[1] Lest there be any misunderstanding, the term "vacate" in this context means to set aside or to void. When the Board vacates an examiner's rejection, the rejection is set aside and no longer exists. Ex parte Zambrano, 58 USPQ2d 1312, 1313 (Bd. Pat. App. & Int. 2001).

Claims 1 and 8 are illustrative of the subject matter on appeal and are reproduced below:

1. A method for disrupting cells comprising:
providing a sonic bath comprising a first liquid;
placing into said first liquid a vessel comprising cells in a second liquid at an alkaline pH; and
subjecting said cells to ultrasonic energy from said sonic bath of sufficient power and duration to cause disruption of said cells in the absence of beads.

8. A method for disrupting cells by applying ultrasonic energy to a sample of cells in a first liquid, wherein the surface tension of said first liquid is reduced.

The references relied upon by the examiner are:

Robbins et al. (Robbins)	3,887,431	Jun. 3, 1975
Robson et al. (Robson)	5,376,527	Dec. 27, 1994

Buck et al. (Buck), "Rapid, Simple Method for Treating Clinical Specimens Containing Mycobacterium tuberculosis To Remove DNA for Polymerase Chain Reaction," J. Clin. Micro., Vol. 30, No. 5, pp. 1331-34 (1992)

The reference relied upon by appellant is:

Murphy et al. (Murphy)	5,374,522	Dec. 20, 1994

GROUND OF REJECTION

Claims 1 and 3-13 stand rejected under 35 U.S.C. § 103 as unpatentable over Buck in view of Robson and Robbins.

DISCUSSION

Buck:

According to the examiner (Answer, page 4), Buck teaches "a method for disrupting Mycobacterium tuberculosis cells using ultrasonic energy without beads" by "providing a sonic bath comprising a first liquid (i.e.[,] dish of water

next to a sonicator probe), and placing into the first liquid a vessel comprising cells in a second liquid (i.e.[,] tubes containing the cells within another liquid, such as residual water or buffer solution or detergent solution)." In addition, the examiner finds that Buck teaches the "use of a liquid having an alkaline pH (i.e.[,] pH 8.3) for disrupting cells..." and describe well know surfactants "Triton X-100 and Tween to be useful for cell disruption."

As we understand the reference, Buck was interested in identifying a methodology for isolating DNA from Mycobacterium tuberculosis for amplification by the polymerase chain reaction. See Title and Abstract. Buck studied four separate methods; (1) treatment with proteinase K and nonionic detergents, (2) boiling with nonionic detergents, (3) freezing and thawing and (4) sonication. For the sonication method, Buck teaches (bridging sentence, pages 1331-1332), "tubes [containing cells suspended in distilled water] were placed in a plastic rack that was floated in a dish of water next to the sonicator probe ... and sonicated for 30 min at 45 W." While the Buck refers to a PCR buffer comprising "a liquid having an alkaline pH," "Triton X-100 and Tween," this PCR buffer was used in methods (1)-(3) above, and was not used in the sonication method taught by Buck. Buck concludes (page 1333, column 1):

> Our results confirm that these simplified methods [(1)-(3) above] are capable of releasing DNA for amplification but suggest that these methods are relatively ineffective, since the sensitivity of detection was only down to about 10^3 organisms.
>
> The sonication procedure, on the other hand, was capable of detecting as few as 10 to 100 organisms. It appears that enough ultrasonic energy is transmitted through the walls of the microcentrifuge tubes to effectively disrupt the mycobacteria.

Robson:

The examiner finds (id., page 4), Robson teaches "disrupting Mycobacteria [sic] cells using sonication, with and without glass beads, and heat at 60°C...." In addition, the examiner finds (id.), Robson teaches "cells to be lysed can be in water, but also can be in suitable buffers having alkaline pH (i.e.[,] Tris-HCl, pH 8.0, pH[] 8.8, etc.)."

As we understand the reference, Robson discloses a "process for lysing mycobacteria ... comprising exposing the bacteria to a lysis effective amount of heat." See Abstract. According to Robson, liberated "DNA is suited for subsequent analysis by way of probe hybridization, restriction enzyme analysis, and the like." Id. Robson discloses (column 1, lines 59-62), "[t]he process of the invention is particularly advantageous since only one step is involved, it is expedient compared to prior processes, and little instrumentation is necessary." By way of seven examples, Robson distinguishes sonication from their heat lysis methodology. In examples 2 and 4 (columns 7-9), Robson discloses the sonication of Mycobacteria tuberculosis with or without glass beads. In each of these examples no, or an insufficient amount of, DNA was released from the cells. In example 5 (column 9), Robson discloses a sonication method with a "GEN-PROBE lysing tube." Robson, however, report (id., at lines 38-41), "[w]hile Gen-Probe was successful, two extra phenol/chloroform extractions were required to clear the sample (i.e.[,] remove contaminants from the lysis solution)

before it was subjected to analysis"[2]. In contrast, Robson discloses in examples 1, 6 and 7 (columns 8, 9 and 10) that their heat treatment methodology released sufficient amounts of DNA.

Robbins:

The examiner finds (Answer, page 5), Robbins teaches "a method for disrupting cells using ultrasonic energy (i.e.[,] sonic disintegration) and adjusting the disrupted cells at an alkaline pH between 8 and 11, and a temperature of 4°C [sic] to 60°C...."

As we understand this reference, Robbins discloses a yeast protein isolate with reduced nucleic acid content and a process of preparing the isolate. See Title and Abstract. While the examiner recognizes that Robbins disrupt cells at "an alkaline pH between 8 and 11" the method of disruption was not by sonication but was instead by homogenization. See column 3, lines 28-47 ("[t]he presently preferred method is homogenization ... in our process the homogenate is adjusted to a pH of above 5.5 preferably between 8 and 11...."). Furthermore, in contrast to the methods of Buck and Robson which were interested disrupting Mycobacterium tuberculosis cells for DNA analysis, for Robbins among "[t]he most important factor[s] is to rupture a majority of the [yeast] cells under conditions such that (1) the endogenous nuclease is not destroyed...." Column 3, lines 25-27. Robbins intended to preserve the activity of the endogenous nuclease activity, because a "principal object [of their invention] is to provide a

[2] We also note that in each sonication example, Robson provide no suggestions of a sonic bath, nor do they identify the power setting of the sonicator used.

process of making a yeast protein isolate in which endogenous nuclease is used to hydrolyze the nucleic acid so that the nucleic acid fragments can be separated from the protein by precipitation of the protein." Robbins, column 2, lines 40-44. To produce a protein isolate with reduced nucleic acid content, Robbins discloses (column 4, lines 3-5), the "incubation of the endogenous nuclease is done at 40°C to 60°C...."

Based on the forgoing analysis of the references of record, we make the following observations.

1. Is Robbins properly combined with Buck and Robson?

As discussed above, it appears that Robbins was interested in hydrolyzing nucleic acid from yeast to produce a yeast protein isolate with reduced nucleic acid content. In contrast, Robson and Buck were interested in disrupting Mycobacteria tuberculosis in order to analyze nucleic acid. It would seem that Robbins' method of hydrolyzing nucleic acid would be inconsistent with the methods of Robson and Buck.

Furthermore, the examiner relies on Robbins to teach, "adjusting the disrupted cells at an alkaline pH between 8 and 11...." Answer, page 5. We emphasize however, that contrary to appellants' claim 1 which requires the cells to be in a liquid at an alkaline pH prior to disruption, Robbins adjust the pH of the homogenate (the material after disruption of the cells). According to Robbins (column 3, lines 28-32), the yeast cells are homogenized at a pH of 4.5-6.5.

In addition, the examiner relies on Robbins to teach "a temperature of 4°C to 60°C (col. 3, lines 18-55)." Answer, page 5. We are unable to identify this temperature range at the section cited by the examiner. Instead, at column 4, lines 3-5, Robbins teaches "[t]he incubation of the endogenous nuclease is done at 40°C to 60°C., a pH of 5 to 8, and for a time of 15 to 120 minutes." As discussed above, this incubation is to hydrolyze nucleic acid present in the preparation, and is therefore inconsistent with the Robson and Buck references. Furthermore, we fail to see the nexus between the recited temperature used for the enzymatic hydrolysis of nucleic acid and the sonication temperature set forth in appellants' claimed invention.

Upon return of the application, the examiner should take a step back and reevaluate whether the references can be properly combined. If the examiner finds that the rejection should be maintained, the examiner should issue an appropriate Office action setting forth such a rejection, using the proper legal standards and clearly explaining the facts relied upon in support of such a rejection.

2. Does Robson teach away from the claimed invention?

In determining whether the claimed invention is obvious, a prior art reference must be read as a whole and consideration must be given where the reference teaches away from the claimed invention. Akzo N.V., Aramide Maatschappij v.o.f. v. United States Int'l Trade Comm'n, 808 F.2d 1471, 1481, 1 USPQ2d 1241, 1246 (Fed. Cir. 1986).

As discussed above, Robson exemplifies several sonication methods that were unable, or required additional purification steps to produce a beneficial result. In contrast to the sonication methods exemplified, Robson exemplifies a single step heat lysis of Mycobacteria tuberculosis that "is particularly advantageous since only one step is involved, it is expedient compared to prior processes, and little instrumentation is necessary." Robson, column 1, lines 59-62. Therefore, it appears that Robson, directs a person of ordinary skill in the art away from sonication methods and toward a method of heat lysis of Mycobacteria tuberculosis.

Upon return of the application, the examiner should take a step back and reevaluate whether the Robson reference in its entirety. If the examiner finds that the rejection should be maintained, the examiner should issue an appropriate Office action setting forth such a rejection, using the proper legal standards and clearly explaining the facts relied upon in support of such a rejection.

3. Surface tension and Buffers.

Appellants' claim 5 further modifies claim 1 by requiring that "the surface tension of said second liquid is reduced." According to the examiner (Answer, pages 5-6):

> [T]he art clearly recognizes the means by which surface tension of liquids may be reduced. Surface tension is reduced by the addition of surfactants. The judicious selection of a surfactant can change the pH conditions of any liquid. This is well known to those of ordinary skill in the art.

> Also since surfactants are well known in the art to reduce surface tension, the reduced surface tension of the liquid containing the cells is the result expected of a liquid containing a surfactant. Thus, the reduced surface tension of the liquid is merely an expected successful result. Because this result is obtained by an obvious modification of the prior art, the reduction in surface tension of the liquid is obvious.

The purpose of this cryptic discussion on surface tension is unclear. It may be that the examiner's statement implies a reference back to her statement (Answer, page 4), "Buck describes Triton X-100 and Tween to be useful for cell disruption. These are well known surfactants in the art." The buffer solutions of Buck, however, were not used in Buck's sonication method. Instead, the cells in Buck's sonication method were suspended in distilled water. Similarily, Robson discloses the use of buffer solutions for their heat lysis method[3], but use water in the sonication methods exemplified.

Therefore, while buffer solutions containing detergents such as Tween 20 are mentioned in Buck and Robson we are unable to identify any suggestion to use these solutions in a method of sonication. While a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the protocol taught by the prior art, the modification is not obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 211 USPQ 1125, 1127 (Fed. Cir. 1984). On this record the examiner identified detergents and buffers in the prior art relied upon but has failed to provide any

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[3] Robson, column 6, lines 26-30 ("[i]n the most basic embodiment of the invention a sample ... containing the intracellular components desired is heated to obtain readily useable components. The organism to be lysed can be in H_2O, but also can be in suitable buffers...and detergents such as 0.5% Tween 20 and 0.5% Nonident P-40.").

explanation as to why a person of ordinary skill in the art would have modified the sonication methods taught by the prior art to include a buffer or detergent.

Upon return of the application, the examiner should take a step back and reevaluate the prior art relied upon. If the examiner finds that the rejection should be made, the examiner should issue an appropriate Office action setting forth such a rejection, using the proper legal standards and clearly explaining the facts relied upon in support of such a rejection.

4. Does Robson teach Mycobacteria tuberculosis is heat resistant?

According to the examiner (Answer, page 7), Mycobacteria tuberculosis "is taught by Robson to be heat resistant (cols. 1-2, all lines)." It appears that the examiner has misapprehended the Robson reference. Contrary to the examiner's statement Robson discloses (column 2, lines 13-22) (emphasis added):

> The heating of Mycobacteria for lysis is advantageous over known methods for lysis of Mycobacteria which involve the use of caustic chemicals, time consuming culturing, and mechanical methods which use the French press, the Hughes press, sonicating probes, bath sonicators, freeze-thawing, glass beads, the Ribi pressure cell, and the like (see Table 1).

Upon return of the application, the examiner should take a step back and reevaluate the prior art relied upon, paying careful attention to exactly what the reference teaches. If the examiner finds that the rejection should be made, the examiner should issue an appropriate Office action setting forth such a rejection, using the proper legal standards and clearly explaining the facts relied upon in support of such a rejection.

For the foregoing reasons, it is our opinion that the examiner did not consider the references relied upon for what they fairly teach a person of ordinary skill in the art. Accordingly, we vacate the pending rejection and remand the application to the examiner for further consideration. We urge the examiner to take this opportunity to reconsider the prosecution history together with the available prior art. If after a renewed consideration of the facts and evidence, the examiner believes that a prior art rejection should be made, the examiner should issue an appropriate Office action setting forth such a rejection, using the proper legal standards and clearly explaining the facts relied upon in support of such a rejection.

We are not authorizing a Supplemental Examiner's Answer under the provisions of 37 CFR § 1.193(b)(1). Any further communication from the examiner which contains a rejection of the claims should provide appellants with a full and fair opportunity to respond.

VACATED and REMANDED

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